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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/029,407	12/26/2001	Larry Caldwell	TOPI-002CIP	3764

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EXAMINER	
GHALI, ISIS A D	

ART UNIT	PAPER NUMBER
1611	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/029,407	CALDWELL ET AL.	
	Examiner	Art Unit	
	Isis A. Ghali	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18 and 24-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18 and 24-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The receipt is acknowledged applicants' amendment and copy of the declaration filed 12/18/2002, both filed 08/01/2008.

Claims 19-23 have been canceled, and claims 29-33 have been added.

Claims 1-18 and 24-33 are pending and included in the prosecution.

Interview Summery

Applicants provided interview summery indicated that the Examiner agreed that the above amendment would overcome the rejection and, if made, the rejection would be withdrawn. However, with reviewing the interview summery dated 14th of July, 2008, the box stated that "agreement was not reaches had been checked. Additionally, the examiner stated in the interview summery that: "The examiner suggested reciting the mechanism of action of NSAID in treating migraine when applied locally to the site of pain." Therefore, no agreement on the current amendment has been made.

The following rejection has been overcome by virtue of applicants' amendment and remarks:

The rejection of claims 1-18 and 24-28 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

The following rejection was discussed in details in the previous office action, and is maintained for reasons of record:

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1-18 and 24-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of either one of the article by Pradalier et al. or the article by Cluff, each article combined with both of US 6,667,799 ('799) and US 5,318,960 ('960).

Pradalier et al. teaches NSAID including ibuprofen, diclofenac and indomethacin having significant effect to treat migraine (see the provided abstract).

Cluff teaches NSAID including ketoprofen and ibuprofen as being beneficial as abortive treatment of migraine (see table 4, and the paragraph preceding table 4 of the provided article).

However, Pradalier and Cluff do not explicitly teach topical application of NSAID as instantly claimed.

US '960 teaches composition for pain relief comprising NSAIDs that when applied to the skin of the patient will deliver pain relieving substance directly to the afflicted area of the body, thus alleviating the side effects caused by systemic application and allowing NSAID to be delivered precisely to the body at specific area of pain (abstract; co1.2, lines 5-9, 61-65). Examples of NSAID include indomethacin, ketoprofen, diclofenac, and ibuprofen (col.3, lines 50, 53, 56; col.6, lines 30, 58).

US '799 teaches method for treatment of host suffering from headache pain with topical application of local anesthetic applied to keratinized skin proximal to target nerves associated with the headache pain, usually to the supraorbital or occipital regions of the head, so the drug penetrates the skin to block conduction in the target nerves and provides pain relief to the host (abstract; col.2, lines 41-67; col.3, lines 1-9;

col.5, lines 18-29, claims). The drug applied topically in formulation comprising cream, plaster or patch (col.4, lines 12-15, 55-57, 66-67; col.5, lines 59-60). The method is used to treat migraine headache (col.6, lines 15-16, 30-35). This method of application of headache pain relief composition to the skin proximal to target nerves associated with the headache is convenient method that is well tolerated by the patient and provides relief of pain shortly after application of the composition (col.6, lines 43-46). This method is improvement over systemic applications of NSAID to treat headache that provides undesired systemic side effects (col.1, lines 17-31).

Therefore, at the time of the invention, NSAIDs including those claimed by applicants were known in the art to be effective and beneficial to treat migraine as taught by Pradalier and Cluff, and NSAID were also known to be delivered topically at the site of pain to alleviating the side effects caused by systemic application and allowing NSAID to be delivered precisely to the body at specific area of pain as taught by US '960, and furthermore, US '799 treated migraine by topical delivery of pain relief composition to keratinized skin proximal to target nerves associated with migraine headache, usually to the supraorbital or occipital regions of the head, so the drug penetrates the skin to block conduction in the target nerves and provides pain relief drug to the host.

Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention to treat migraine using NSAID as disclosed by any of Pradalier or Cluff, and deliver NSAID topically directly to the site of pain to alleviating the side effects caused by systemic application and allowing NSAID to be delivered precisely to

specific area of pain as taught by US '960, and further deliver NSAID to keratinized skin proximal to target nerves associated with migraine headache specifically to the supraorbital or occipital regions of the head, so the drug penetrates the skin to block conduction in the target nerves and provides pain relief to the host by convenient well tolerated method as disclosed by US '799, with reasonable expectation of treating migraine headache by topically applying NSAID to keratinized skin proximal to target nerves associated with migraine headache to the supraorbital or occipital regions of the head to block conduction in the target nerves and effectively relief migraine without having undesired systemic side effects of NSAID wherein the method is convenient and well tolerated by the patient and provides relief of pain shortly after application of NSAID.

Regarding the amounts of NSAID recited in claims 29 and 30, the amount does not impart patentability to the claims, absent evidence the contrary. One having ordinary skill in the art the time of the invention would have determined the dose of the drug according to the severity of condition to be treated, patient age, and the specific formulation delivering the drug.

Response to Arguments

4. Applicant's arguments filed 08/01/2008 have been fully considered but they are not persuasive.

Applicants traverse this rejection by arguing that mechanism of action of local anesthetic is different from the mechanism of action of NSAID.

In response to this argument, it is argued that the mechanism of action is not claimed and Caldwell reference ('799) is relied upon for teaching treating migraine by topical delivery of pain relief composition to keratinized skin proximal to target nerves associated with migraine headache, and its teaching to specific sites of application of the drug composition to treat migraine.

Applicants argue that the combination of references fails to teach each and every element of the rejected claims that are directed to treating a headache with a topical NSAID formulation which provides only local effect (not systemic) of the active agent of the topical formulation that is responsible for the treatment effect. This element of "topically applying an effective amount of a topical NSAID formulation" of the claims is neither taught nor suggested in any of the cited combination of references nor can this invention be predicted from their combined teachings. The cited primary references of Pradilier and Cluff are silent with respect to topically applying a topical NSAID formulation as claimed and Toppo is directed to an NSAID composition for relief of arthritis-related pain. Toppo does not describe the utility of a topical NSAID applied to the keratinized skin of the head to relieve headache. The inventors of the present application found that, contrary to the accepted belief of those of ordinary skill in the art at the time the application was filed, one could treat the migraine headaches and indomethacin responsive headaches and reduce the pain felt in the brain by applying a topical NSAID formulation to a keratinized skin surface of the head, e.g., the forehead

and/or temple, resulting in only local action of the NSAID. Caldwell is directed to a pain relief composition that includes a local anesthetic.

In response to this argument, it is argued that the invention as whole is taught by the combination of the references. At the time of the invention, it would have been prima facie obvious to combine the references to arrive to the claimed invention in view of the cited references. The examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, at the time of the invention, NSAIDs including those claimed by applicants were known in the art to be effective and beneficial to treat migraine as taught by Pradilier and Cluff, and NSAID were also known at the time of the invention to be delivered topically at the site of pain to alleviating the side effects caused by systemic application and allowing NSAID to be delivered precisely to the body at specific area of pain as taught by US Toppo and as desired by applicants, and furthermore, US Caldwell treated migraine by topical delivery of pain relief composition to keratinized skin proximal to target nerves associated with migraine headache, supraorbital or occipital regions of the head, so the drug penetrates the skin and acts locally at the site of the pain and provides pain relief to the host. Toppo is not directed to treatment of arthritis as applicants assert. Toppo is directed to composition for transdermal delivery of pain reliving substances directly to afflicted

areas of the body (see col.1, lines 7-11; col.2, lines 5-10). Caldwell is relied upon for teaching that migraine headache can be treated by applying the drug effective to treat migraine pain at keratinized skin of the forehead or the temporal area. Mechanism of action of the drug does not matter as long it is absorbed through the skin and contact the underlying tissues and exerts its action locally at this tissues including nerves, blood vessels and muscles underlying the skin. Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention to treat migraine using NSAID as disclosed by any of Pradilier or Cluff, and deliver NSAID topically directly to the site of pain to alleviating the side effects caused by systemic application and allowing NSAID to be delivered precisely to specific area of pain as taught by US '960, and further deliver NSAID to keratinized skin proximal to target nerves associated with migraine headache specifically to the supraorbital or occipital regions of the head, so the drug penetrates the skin to the underlying tissues and provides pain relief to the host by convenient well tolerated method as disclosed by US '799. In considering the disclosure of the reference, it is proper to take into account not only the specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom. *In re Preda*, 401 F.2d 825, 826, 159 USPQ 342, 344 (CCPA 1968). The rational to modify or to combine the prior art does not have to be expressly stated in the prior art; the rational may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art. The reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve

different problem. It is not necessary that the prior art suggest the combination or modification to achieve the same advantage or result discovered by applicant. *In re Linter*, 458 F.2d 1013, 173 USPQ 560 (CCPA 1972).

Applicants argue that the combination of the cited references fails to provide one of skill in the art with predicted success in the claimed invention. Demonstrating that all elements were known in the prior art does not provide evidence that the combination would be "a predicted success".

In response to this argument, it is argued that the cited references show that it was well known in the art at the time of the invention to use NSAID to treat migraine, and also showed that NSAID can be applied at the site of pain, and further showed that migraine that has central origin is treated by applying the treating drug locally at the site of headache at the forehead or temporal area. Based on the disclosure by these references, an artisan of ordinary skill would have a reasonable expectation that a combination of these references would provide reasonable success. No patentable invention resides in combining old ingredients/method of known properties/effect where the results obtained thereby are no more than the additive effect. See *In re Sussman*, 1943 C.D. 518; I*n re Huellmantel* 139 USPQ 496; *In re Crockett* 126 USPQ 186. It has been held that “When a patent simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the combination is obvious.” *KSR Int 'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1740 (2007) (quoting *Sakraida v. AG Pro, Inc.,* 425 U.S. 273,282

(1976)). "When the question is whether a patent claiming the combination of elements of prior art is obvious," the relevant question is "whether the improvement is more than the predictable use of prior art elements according to their established functions." In addition, "To determine whether there was an apparent reason to combine the known elements in the way a patent claims, it will often be necessary to look to interrelated teachings of multiple patents; to the effects of demands known to the design community or present in the marketplace; and to the background knowledge possessed by a person having ordinary skill in the art. To facilitate review, this analysis should be made explicit. But it need not seek out precise teachings directed to the challenged claim's specific subject matter, for a court can consider the inferences and creative steps a person of ordinary skill in the art would employ". Pp. 11-14. KSR INTERNATIONAL CO. v. TELEFLEXINC. ET AL. (2007).

It is well established that the claims are given the broadest reasonable interpretation during examination in light of the supporting disclosure as it would be interpreted by one of ordinary skill in the art, *In re Morris,* 127 F.3d 1048, 1054-55, 44 USPQ2d 1023,1027-28 (Fed. Cir. 1997); *In re Am. Acad. of Sci. Tech. Ctr.*, 367 F.3d 1359,1364[, 70 USPQ2d 1827] (Fed. Cir. 2004). Further, it has been held that the words of the claim must be given their plain meaning unless the plain meaning is inconsistent with the specification. *In re Zletz*, 893 F.2d 319, 321, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989); *Chef America, Inc. v. Lamb-Weston, Inc.*, 358 F.3d 1371, 1372, 69 USPQ2d 1857 (Fed. Cir. 2004). In the present case, the reasonable interpretation of the claims would be treating migraine headache by topically applying NSAID to skin

proximal to site associated with migraine headache which is the supraorbital or occipital regions of the head. The reasonable prediction from the combined teachings of the cited references would be treating migraine headache by topically applying to the site of headache, which is usually the forehead and the temporal area, a composition comprising NSAID, with a reasonable expectation of effective relief migraine headache without having undesired systemic side effects of NSAID wherein the method is convenient and well tolerated by the patient and provides relief of pain shortly after application of NSAID.

In the light of the foregoing discussion, the Examiner's ultimate legal conclusion is that the subject matter defined by the claims would have been prima facie obvious within the meaning of 35 U.S.C. 103 (a). The invention as a whole is taught by the combined teachings of the cited references.

Response to Amendment

5. The declaration under 37 CFR 1.132 filed 12/10/2002 is insufficient to overcome the rejection of claims 1-18 and 24-33 based upon U.S.C. 103 (a) over the combination of Pradilier, Cluff, Toppo and Caldwell as set forth in the last Office action because: according to applicants the declaration showed that the common belief in the relevant art at the time of the invention was that a topical formulation of an NSAID that is effective by acting only locally would not be able to supply a therapeutically effective level of the NSAID sufficient to treat a headache and that only local peripheral action of an NSAID drug applied to the skin of the head would not treat headache pain. The

present invention is based on discovery of the unexpected result that a topical formulation of an NSAID applied to the keratinized skin of the head does indeed provide a therapeutically effective method of treating headaches. However, it is the position of the examiner that the declaration was directed only to indomethacin responsive headache and to one specific species indomethacin, and therefore, the declaration refer(s) only to the system described in the above referenced application and not to the individual claims of the application. The claims are directed to NSAID that encompasses many drugs that differ radically in their structure and behavior, and not all NSAID will have the same ability to penetrate the skin. Each NSAID drug requires different formulation to enable its topical delivery according to its nature. For example, hydrophilic drugs need different formulation than that needed by hydrophobic, and basic drugs need different formulation than that needed by acidic drugs. Thus, there is no showing that the objective evidence of nonobviousness is commensurate in scope with the claims. See MPEP § 716.

Conclusion

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Isis A. Ghali whose telephone number is (571) 272-0595. The examiner can normally be reached on Monday-Thursday, 6:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau can be reached on (571) 272-0614. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

IG

/Isis A Ghali/
Primary Examiner, Art Unit 1611